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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,353	KRIEG ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/12/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,29,31-33 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-29, 31-33 AND 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 12, 2009 has been entered.

The declaration filed on 3/12/2009 by Cy Stein is not considered.

Amendment Entry

2. The amendment filed October 23, 2007 has been entered. Claims 28-29, 31-33, and 36 are pending and under examination. Claims 28-29 have been amended.

Withdrawal of Rejection

3. The rejection of claims 28 and 36 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 101, 107-109, 120-122, 124 of copending Application No. 10/314,578 has been withdrawn in view of applicants amendments.

4. The rejection of claims 28-29, 31-33, and 36 under 35 U.S.C. 103(a) as being unpatentable over Kataoka et al 1992 Jpn. J. Cancer Res. Vol. 83 pgs. 244-247 in view of Goodchild et al 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al US Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994) has been withdrawn in view of applicants amendments.

Response to Arguments

5. Applicant's arguments with respect to claims 28-29, 31-33, and 36 have been considered but are moot in view of the ground(s) of rejection.

Claim Rejections Maintained - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The rejection of claims 28-29, 31-33, and 36 under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al 1992 Jpn J. Cancer Res Vol. 83 pgs. 1128-1131 in view of Goodchild et al 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al US Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994) is maintained for the reason set forth in the previous office action.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 103(a), March 12, 2009 is carefully considered, but not found to be persuasive for the reasons below.

A) Applicants states the Examiner has dismissed Applicant's arguments and that the references previously cited by Applicant have not been addressed.

B) Applicants argue that it was not known in the art that phosphorothioate backbones should be used with immunostimulatory oligonucleotides and that a change in backbone would affect the properties of the immunostimulatory oligonucleotides. In support of Applicant's arguments a Declaration of Dr. Cy Stein is enclosed herewith.

C) It is further stated in the Advisory Action that Hutcherson et al teach that phosphorothioate ODN analogs enhance immune stimulation. However, the skilled artisan would not have modified the ODN of Kuramoto et al to add phosphorothioate linkages based on the teachings of Hutcherson because the teachings of the two references are inconsistent and further in view of the known unpredictability of the phosphorothioates in the art, as discussed above. Kuramoto et al teach that the immunostimulatory DNA is sequence specific and is representative of immunostimulatory bacterial DNA. Bacterial DNA is not phosphorothioate modified. Kuramoto et al further teach that the immunostimulatory activity of the ODN is due to the hexameric palindrome within the sequence. Hutcherson describes generally that phosphorothioate ODN analogs can provoke an immune stimulatory response. However, Hutcherson does not provide any teaching regarding inclusion of a palindrome. In fact, Hutcherson et al. teaches that it is the phosphorothioate internucleotide linkage that has immunostimulatory activity. The skilled artisan attempting to create a synthetic version of bacterial DNA that was immunostimulatory would not have been motivated to phosphorothioate modify it because oft he teachings of Hutcherson. Hutcherson is describing molecules that are distinct from Kuramoto et al in that they are phosphorothioate modified and are sequence independent.

Examiner's Response to arguments:

In response to applicant's statement in (A), Applicants argue that the references previously cited by Applicant have not been addressed. Examiner disagrees, Applicants arguments were addressed in the prior office action on 9/12/2008 specifically pgs. 4-14.

In response to applicant's statement in (B), the submitted document as noted in Applicant's argument as the Declaration of Dr. Cy Stein is not considered. It include(s) statements which amount to an affirmation that the affiant has never seen the claimed subject matter before. The Declaration of Dr. Cy Stein is insufficient to overcome the rejection based upon it was a declaration made in the prosecution of another case and was not properly executed for use in the application. This is not relevant to the issue of

nonobviousness of the claimed subject matter and provides no objective evidence thereof. See MPEP § 716. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

In response to applicant's statement in (C), Kuramato et al discloses an oligonucleotide comprising AACGTT as disclosed in the specification. Kuramato et al teach the function of the oligonucleotide is to induce NK cell activity as stated in the specification. Therefore, the oligonucleotide of Kuramato et al is functionally identical to the oligonucleotide as claimed. Although Kuramato does not specifically teach the use of phophorothioate phosphate backbone, Kuramato et al teach that the pharmacologic properties of the oligonucleotide are dependent on the oligonucleotide, not on method of synthesis. However, Hutcherson et al teach that phosphorothioate ODN analogs enhance immune stimulation. Thus, the skilled artisan would have modified the ODN disclosed by Kuramoto et al by adding phosphorothioate linkages based on the teachings a method of administering phosphorothioate oligonucleotide analogs which produce a localized immune stimulation and for enhancing the efficacy of antiinfective and anticancer agents (see abstract) as taught by Hutcherson et al.

As outlined previously, the instant claims are drawn to an oligonucleotide, comprising: 5'-AACGTT-3', 8-40 nucleotides in length, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate.

Kuramato et al teach an oligonucleotide, comprising: 5'-AACGTT-3', 8-40 nucleotides in length.

Kuramoto et al teach that all oligonucleotide used were synthesized by the standard phosphoramidite method using an automatic DNA synthesizer.

Kuramato et al does not teach an oligonucleotide wherein internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate, and having at least one phosphate backbone modification, wherein the oligonucleotide is linked to a nucleic acid delivery complex, wherein the oligonucleotide is covalently linked to the nucleic acid delivery complex, wherein the nucleic acid

delivery complex is a cationic lipid, wherein the nucleic acid delivery complex is sterol. Kuramoto et al does not teach a composition of comprising the oligonucleotide and a pharmaceutically acceptable carrier.

Goodchild et al teaches an oligonucleotide wherein the phosphate backbone modification is a phosphorothioate (see pg. 167 column 1 last paragraph, column 2 last paragraph). Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA to enzymatic degradation (see pg. 167 "Synthesis of Modified Oligonucleotides", pg. 175 "The Effect of Modification on Nuclease Resistance"). Goodchild et al. teaches that shorter oligonucleotides are taken up more rapidly (see pg. 176 column 1 paragraph 5).

Hutcherson et al teach a composition (see column 5 lines 40-67, column 6 lines 31-43, column 7 lines 55-67, column 10 lines 46-57) comprising: an oligonucleotide delivery complex, wherein the oligonucleotide delivery complex contains an immunostimulatory CpG containing oligonucleotide associated (covalently) with a cationic lipid, wherein the CpG includes a phosphate backbone modification is a phosphorothioate (see abstract, column 5 lines 40-59, column 8 lines 31-50). Hutcherson et al teach a composition comprising a pharmaceutically acceptable carrier (see column 7 lines 49-55), wherein the oligonucleotide is synthetic (see column 8 lines 32-41).

Cheng et al teach oligonucleotides having phosphorothioate linkage covalently linked to a sterol.

It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Kuramato et al by modifying the backbone and inclusion of linking the oligonucleotide in a delivery complex according to Hutcherson et al to because Hutcherson et al teaches that cationic lipids can significantly enhance the uptake and fate of oligonucleotides. It would also have been prima facie obvious to modify the backbone of the oligonucleotide of Kataoka et al to include phosphorothioate taught by Goodchild et al because Goodchild et al teaches that the backbone modifications prevent degradation by nucleases and increase or improve uptake (see section B pg. 167). It would have been prima facie obvious at the time the invention was made to modify the

oligonucleotide of Kuramoto et al by inclusion of a sterol because both Cheng et al and Kuramato both teach oligonucleotide in a delivery complex.

New Grounds of Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 28-29, 31-33, and 36 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 19 and 21 of copending Application No. 10/956,745 in view of Oberhauser et al. 1992 Nucleic Acids Research vol 20 p. 533-538 and Hutcherson et al US 5,723,335 1998 (continuation of serial no 217,988, March 25, 1994), and Sonehara et al (J. Interferon and Cytokine Research, 1996, 16:799-803)

The instant claims are drawn to an oligonucleotide, comprising 5'-AACGTT-3', 8-40 nucleotides in length, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone modification, wherein the

phosphate backbone modification is a phosphorotihioate (claim 28), an oligonucleotide, comprising: 5'-AACGTT-3', 8-40 nucleotides in length, and having at least one phosphate backbone modification, wherein the oligonucleotide is linked to a nucleic acid delivery complex (claim 29), wherein the oligonucleotide is covalently linked to the nucleic acid delivery complex (claim 31), wherein the nucleic acid delivery complex is a cationic lipid (claim 32), wherein the nucleic acid delivery complex is a sterol (claim 33); a composition comprising the oligonucleotide of claim 28 and a pharmaceutically acceptable carrier.

The U.S. Application of 10/956,745 claims are drawn to a composition comprising an immunostimulatory oligonucleotide, a pharmaceutically acceptable carrier an antigen, wherein the immunostimualtory oligonucleotide is 8-100 nucleotides in length, wherein the immunostimulatory of oligonucleotide comprises AACGTT, wherein the immunostimulatory oligonucleotide includes a phosphate backbone modification, and wherein the immunostimulatory oligonucleotide promotes a Th1 type response and a cytotoxic lymphocyte response in a subject when administered in conjunction with the antigen (claim 19), wherein the phosphate backbone modification is selected from the group consisting of a phosphorothioate and a phosphorodithioate modification (claim 21).

The US Application of 10/956,745 does not teach that the immunostimulatory CpG containing oligonucleotides are linked to a nucleic acid delivery complex (claims 29 and 31 of 10/789353), wherein the nucleic acid delivery complex is a cationic lipid (claim 32 10/789353), wherein the nucleic acid delivery complex is a sterol (claim 33 10/789353).

Oberhauser teach that oligonucleotides linked to phospholipids and cholesterol show an enhanced association with cultured cells and teaches that oligonucleotides thiocholesterol conjugates containing a bioreversible disulfide linkage have enhanced affinity for and internalization into cells (p. 533, left column under introduction).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the CpG containing oligonucleotides of the 10/956745 application as suggested by Oberhauser et al to link said oligonucleotides to a nucleic acid delivery complex such as a lipid or sterol because Oberhauser et al teach that said complexes

enhance the affinity of said oligonucleotides for and internalization into cells thus resulting in the instant claimed invention with a reasonable expectation of success.

Furthermore, the US Application of 10/956745 claims do not teach a composition in conjunction with an antigen promoting Th1 type response and a cytotoxic lymphocyte response in a subject (claim 19 of 10/956745).

Hutcherson et al teach the administration of an oligonucleotide in a pharmaceutical carrier to subjects in conjunction with therapeutic modalities such as tissues or cells by a bacterium or virus (see column 5 lines 55-67 and column 6 lines 1-11) which result in a the release of cytokines IL-1 alpha (see claims 1-3).

Sonehara et al discloses an immunostimulatory oligonucleotide of 8-100 nucleotides in length having phosphate backbone modifications (abstract, tables 3 and 4). Sonehara et al discloses octamers, decamers, 12-mers, 16-mers and 18-mers that showed increases in interferon (table 5) when added with cationic liposomes (see abstract), which is an indication of promotion of the Th-1 response. Sonehara et al discloses the immunostimulatory oligonucleotide comprising the sequence AACGTT (abstract) Sonehara et al discloses that the oligonucleotides were synthesized on an automatic synthesizer by the phosphoramidite method, i.e. phosphate backbone modifications (materials and methods, pp. 799-800). Oligo-B, which is a 30-mer, has a phosphorothioate modification (p. 800). Table 2 indicates that the oligonucleotide contained nucleotides (i.e. C) that were unmethylated (see also p. 802, right column).

Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705,709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty."). MPEP 2100.

The prior art of Sonehara et al anticipates the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicants' immunostimulatory oligonucleotide with the immunostimulatory oligonucleotide of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed immunostimulatory oligonucleotide and the immunostimulatory oligonucleotide of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the CpG containing oligonucleotide of the US Application 10/956745 application as suggested by Sonehara et al to incorporate the composition in conjunction with an antigen promoting Th1 type response and a cytotoxic lymphocyte response in a subject (claim 19 of 10/956745) because Sonehara et al teach the encapsulation of an oligonucleotide containing AACGTT in liposomes significantly enhanced there activity to induce interferon activity thus resulting in the instant claimed invention with a reasonable expectation of success.

Thus the instant claims (28-29, 31-33, and 36) encompassing an oligonucleotide, comprising 5'-AACGTT-3', 8-40 nucleotides in length, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone modification, wherein the phosphate backbone modification is a phosphorotihioate are obvious over claims 19 and 21 of copending Application No. 10/956,745.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina Archie
Examiner
Art Unit 1645

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645